## ESM Table 1. Results in the individual cohorts

| | Hoorn study Cohort | | | | | Utrecht Cohort | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low (≤6 risk alleles) | Medium (7-8 risk alleles) | High (≥9 risk alleles) | $p_{\mathrm{unadj}}$ | $p_{\mathrm{adj}}$ | Low (≤6 risk alleles) | Medium (7-8 risk alleles) | High (≥9 risk alleles) | $P_{\mathrm{unadj}}$ | $p_{\mathrm{adj}}$ |
| *N* (NGT/IGT) | 43 (43/0) | 63 (63/0) | 36 (36/0) | | | 19 (14/5) | 33 (29/4) | 20 (17/3) | | |
| Age (years) | 61±1 | 61±1 | 59±1 | 0.26 | | 47±2 | 45±1 | 49±1 | 0.17 | |
| Sex (male/female) | 19/24 | 34/29 | 13/23 | 0.22 | | 3/16 | 10/23 | 4/16 | 0.46 | |
| BMI (kg/m$^2$) | 28.0±0.6 | 28.0±0.5 | 27.7±0.6 | 0.94 | | 26.7±0.9 | 25.2±0.7 | 26.2±0.7 | 0.39 | |
| First-phase insulin secretion (pmol/l) | 691 (409–956) | 587 (375–900) | 488 (352–733) | 0.23 | 0.14 | 954 (738–1332) | 780 (564–1023) | 852 (372–1073) | 0.09 | $5.7*10^{-4}$ |
| Second-phase insulin secretion (pmol/l) | 220 (186–352) | 257 (169–342) | 238 (141–389) | 0.89 | 0.63 | 278 (194–366) | 246 (183–320) | 281 (215–341) | 0.96 | 0.84 |
| Insulin sensitivity index (μmol min$^{-1}$ kg$^{-1}$ [pmol/l]$^{-1}$) | 0.10 (0.07–0.16) | 0.10 (0.07–0.17) | 0.12 (0.08–0.18) | 0.63 | 0.39 | 0.17 (0.12–0.30) | 0.18 (0.11–0.28) | 0.19 (0.14–0.27) | 0.95 | 0.90 |
| Disposition index (μmol min$^{-1}$ kg$^{-1}$) | 69 (43–94) | 66 (45–111) | 59 (38–89) | 0.54 | 0.46 | 213 (93–242) | 143 (91–206) | 154 (79–192) | 0.24 | $7.2*10^{-3}$ |

| | Tübingen study Cohort | | | | | NTR Twin study Cohort | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low (≤6 risk alleles) | Medium (7-8 risk alleles) | High (≥9 risk alleles) | $p_{\mathrm{unadj}}$ | $p_{\mathrm{adj}}$ | Low (≤6 risk alleles) | Medium (7-8 risk alleles) | High (≥9 risk alleles) | $p_{\mathrm{unadj}}$ | $p_{\mathrm{adj}}$ |
| *n* (NGT/IGT) | 34 (28/8) | 47 (36/11) | 37 (19/18) | | | 46 (45/1) | 43 (39/4) | 31 (29/2) | | |
| Age (years) | 40±3 | 35±2 | 44±2 | 0.007 | | 32±1 | 31±1 | 31±1 | 0.64 | |
| Sex (male/female) | 15/19 | 22/25 | 14/13 | 0.71 | | 21/25 | 22/21 | 12/19 | 0.58 | |
| BMI (kg/m$^2$) | 25.9±0.9 | 24.8±0.8 | 26.2±0.9 | 0.44 | | 24.0±0.6 | 24.3±0.5 | 24.0±0.6 | 0.92 | |
| First-phase insulin secretion (pmol/l) | 928 (510–1198) | 658 (478–1119) | 568 (421–892) | 0.06 | 0.02 | 887 (634–1334) | 844 (592–1233) | 679 (520–839) | 0.06 | $9.4*10^{-4}$ |
| Second-phase insulin secretion (pmol/l) | 226 (156–346) | 238 (161–346) | 197 (137–302) | 0.43 | 0.38 | 219 (157–363) | 218 (177–380) | 213 (162–305) | 0.40 | 0.5 |
| Insulin sensitivity index (μmol min$^{-1}$ kg$^{-1}$ [pmol/l]$^{-1}$) | 0.13 (0.09–0.20) | 0.12 (0.08–0.17) | 0.13 (0.08–0.22) | 0.82 | 0.49 | 0.20(0.15–0.31) | 0.23 (0.12–0.32) | 0.23 (0.13–0.34) | 0.85 | 0.33 |
| Disposition index (μmol min$^{-1}$ kg$^{-1}$) | 104(68–176) | 91 (57–155) | 74 (53–113) | 0.03 | 0.10 | 182 (137–256) | 178 (148–223) | 167 (108–199) | 0.10 | 0.039 |

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|---|---|---|---|---|---|---|---|---|---|---|
| **Other non-glucose secretagogues** | | | | | | | | | | |
| GLP-1 stimulated IS (pmol $l^{-1}$) | 2941 (2065–5465) | 2865 (1905–4110) | 2021 (1093–2937) | 0.01 | $9.7*10^{-4}$ | 1177(617–2365) | 1162 (794–2587) | 1184 (726–2043) | 0.75 | 0.40 |
| Arginine stimulated IS (pmol $l^{-1}$) | 2308 (1927–4242) | 2405 (1217–3145) | 1876 (1573–2752) | 0.06 | 0.29 | 2245 (1368–2787) | 2054 (1734–3032) | 1888 (1175–3001) | 0.43 | 0.84 |
| Peak level Arginine (pmol/l) | 6784 (5339–11911) | 5957 (4218–8167) | 4970 (3280–7167) | 0.28 | 0.02 | 4529 (2670–7154) | 4639 (3085–6939) | 3868 (2627–5797) | 0.59 | 0.89 |

Data are unadjusted mean ± SEM or median (interquartile range). Insulin secretion, insulin sensitivity index and disposition index were log-transformed before analysis
The table shows *p* values using an additive regression model, unadjusted ($p_{unadj}$) and adjusted ($p_{adj}$) for age, sex, BMI, ISI (were appropriate) and glucose tolerance status.

Supplementary table 2. Association results for the eight single genes

| **Gene** | **RAF** | **First-phase insulin response (pmol/l)** | **Second-phase insulin response (pmol/l)** | **Insulin sensitivity index (µmol/min/kg/ pmol/l)** | **Disposition index (µmol/min/kg)** | **GLP-1 stimulated insulin release* (pmol/l)** | **Arginine stimulated insulin release* (pmol/l)** |
|---|---|---|---|---|---|---|---|
| *TCF7L2,* rs7903146 [†] | | | | | | | |
| β | 0.32 | 0.95 (0.89;1.02) | 1.02 (0.96;1.09) | 1.09 (0.99;1.19) | 1.00 (0.93;1.07) | 1.02 (0.89;1.16) | 0.97 (0.87;1.09) |
| P | | 0.18 | 0.48 | 0.07 | 0.95 | 0.81 | 0.67 |
| *KCNJ11*, rs5219 [‡] | | | | | | | |
| β | 0.37 | 0.96 (0.89;1.03) | 0.98 (0.92;1.04) | 1.03 (0.95;1.11) | 0.96 (0.91;1.05) | 0.94 (0.83;1.06) | 0.97 (0.89;1.05) |
| P | | 0.22 | 0.49 | 0.49 | 0.56 | 0.32 | 0.44 |
| *CDKAL1*, rs7754840 [§] | | | | | | | |
| β | 0.33 | 0.89 (0.83;0.95) | 0.98 (0.92;1.04) | 0.96 (0.89;1.04) | 0.86 (0.80;-0.93) | 0.94 (0.83;1.06) | 0.96 (0.86;1.06) |
| P | | $6.3*10^{-4}$ | 0.45 | 0.33 | $1.5*10^{-4}$ | 0.31 | 0.42 |
| *IGF2BP2*, rs4402960 [§] | | | | | | | |
| β | 0.31 | 0.94 (0.87;1.00) | 0.96 (0.91;1.02) | 1.05 (0.98;1.12) | 0.97 (0.91;1.05) | 0.86 (0.75;0.99) | 0.95 (0.86;1.04) |
| P | | 0.05 | 0.16 | 0.16 | 0.49 | 0.04 | 0.24 |
| *HHEX/IDE,* rs1111875 [§] | | | | | | | |
| β | 0.60 | 0.94 (0.88;1.00) | 0.97 (0.92;1.03) | 1.06 (0.98;1.15) | 0.96 (0.89;1.03) | 1.00 (0.89;1.14) | 1.02 (0.93;1.11) |
| P | | 0.07 | 0.40 | 0.17 | 0.26 | 0.94 | 0.74 |
| *SLC30A8,* rs13266634 [§] | | | | | | | |
| β | 0.72 | 0.97 (0.90;1.04) | 0.99 (0.93;1.05) | 1.07 (0.98;1.16) | 1.02 (0.94;0.91) | 0.97 (0.84;1.11) | 0.96 (0.87;1.06) |
| P | | 0.38 | 0.69 | 0.13 | 0.64 | 0.63 | 0.43 |
| *CDKN2A/B,* rs10811661 [§] | | | | | | | |
| β | 0.81 | 1.01 (0.93;1.10) | 1.03 (0.97;1.11) | 0.94 (0.85;1.03) | 0.98 (0.89;1.07) | 1.08 (0.94;1.24) | 1.06 (0.95;1.19) |
| P | | 0.83 | 0.37 | 0.18 | 0.63 | 0.29 | 0.31 |
| *MTNR1B,* rs10830963 [‖] | | | | | | | |
| β | 0.26 | 0.92 (0.86;1.02) | 1.03 (0.97;1.09) | 0.96 (0.88;1.05) | 0.90 (0.84;0.97) | 1.12 (0.99;1.27) | 1.07 (0.99;1.17) |
| P | | 0.01 | 0.40 | 0.37 | $4.9*10^{-3}$ | 0.07 | 0.10 |

Data are represented as β's (95% CI). RAF, risk allele frequency. All variables were log-transformed before analysis. β and P-values were computed for additive models using linear generalized estimating equations (GEE) which takes into account the family relatedness when computing the standard errors. 1st and 2nd phase GSIS, GLP-1 and arginine stimulated insulin secretion were adjusted for study center, family relatedness, glucose tolerance status, age, gender, BMI and ISI. ISI and DI were adjusted for study center, family relatedness, glucose tolerance status, age, gender and BMI. *available for 224 subjects from the Tübingen and NTR twin sample. [†] Data for the Hoorn, Utrecht and Tübingen samples originate from 't Hart et al. (16), [‡] Tschritter et al and 't Hart et al. (14,15) and [§] Groenewoud et al. (17). [‖] Data for the Dutch samples from Simonis-Bik et al. Manuscript submitted to Diabetes (DB09-1048). Data from the Tübingen study are from Staiger et al. (30).

**Supplementary figure 1. Distribution of risk alleles in the study sample.**